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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/448,378	11/23/1999	KENNETH BRASEL	2836-US-DIV	4973

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EXAMINER	
GAMBEL, PHILLIP	

ART UNIT	PAPER NUMBER
1644	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

TH

Office Action Summary	Application No.	Applicant(s)	
	09/448,378	BRASEL ET AL.	
	Examiner	Art Unit	
	Phillip Gambel	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 November 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *6,7,20,22-24,28,30-35 and 40-53* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *6,7,20,22-24,28,30-35 and 40-53* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment, filed 11/19/2007, has been entered.
Claims 6 and 20 have been amended.

Claims 1-5, 8-19, 21, 25-27, 29, 36-39 and 54-56 have been canceled previously.

Claims 6, 7, 20, 22-24, 28, 30-35 and 40-53 are pending.
Applicant's election without traverse of Group I and the species GM-CSF has been acknowledged.

2. The text of those sections of Title 35 USC not included in this Action can be found in a prior Office Action.

This Office Action will be in response to applicant's amendment, filed 11/19/2007.

The rejections of record can be found in the previous Office Actions.

3. Applicant's amended claims, filed 11/19/2007, have obviated the previous rejection under 35 U.S.C. § 112, first paragraph, written description / new matter with respect to the recitation of "for a duration of time".

4. Claims 1-10 and 12-17 are rejected under 35 U.S.C. § 112, first paragraph, as the specification does not contain a written description of the claimed invention, in that the disclosure does not reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention at the time the application was filed.
The specification as originally filed does not provide support for the invention as now claimed: "for a period of 14 to 19 days".

Applicant's amendment and argument, filed 11/19/2007, does not appear to provide sufficient written support to the newly added claim recitation of "for a period of 14 to 19 days".

Applicant relies upon the teachings in Example 1 and Example 3 of the instant specification for the newly added claim recitation of "for a period of 14 to 19 days".

Example 1: Generation of Dendritic Cells.

This Example describes a method for using flt3-1igand to generate large numbers of dendritic cells ex vivo. Cells having the $CD34^+$ phenotype are isolated as described above, for example, first by generating a buffy coat of cells using a procedure described supra. Cells from the buffy coat are then incubated with a CD34 specific monoclonal antibody. The $CD34^+$ cells which are selected then are cultured in McCoy's enhanced media with 20 ng/ml each of GM-CSF, IL-4, TNF-α, or 100 ng/ml flt3-1igand or c-kit ligand. The culture is continued for approximately two weeks at 37 *C in 10% CO2 in humid air. Cells then are sorted by flow cytometry for $CDla^+$ and $HLA\text{-}DR^+$ expression. **The combination of GM-CSF, IL-4 and TNF-α, resulted in a six to seven-fold increase in the number of cells obtained after two weeks of culture. The combination of flt3-1igand and c-kit ligand resulted in an additive 12-13-fold increase in absolute cell numbers.** This correlated with an 18-fold expansion with either flt3-1igand or c-kit ligand or to a 34-fold expansion with the combination of fh3-1igand and c-kit ligand. Phenotypic analysis of the cells showed that between 60-70% of the cells were $HLA\text{-}DR^+$, $CD86^+$, with 40-50% of the cells expressing CDla in all factor combinations examined. The addition of flt3-1igand increased the absolute number of $CDla^+$ cells by 5-fold. c-Kit ligand increased those cells by 6.7- fold and the combination of flt3-1igand and c-kit ligand by 11-fold. Functional analysis of the resultant cells in an MLR revealed that the presence of flt3-1igand or c-kit ligand did not affect the stimulatory capacity of the resultant dendritic cells while increasing the numbers attained.

Example 3: Use of Flt3-L in Augmenting Anti-tumor Immune Responses.

This Example describes a method for using flt3-L to augment anti-tumor immune responses in vivo. Female C57BL/10J (B 10) mice (The Jackson Laboratory, Bar Harbor, ME) were injected with 5 x 105 viable B10.2 or B10.5 fibrosarcoma tumor cells by intradermal injection in a midline ventral position in a total volume of 50 µl. The fibrosarcoma B 10.2 and B 10.5 lines are of B 10 origin and have been described previously, see Lynch et al., Euro. J. Immunol., 21:1403 (1991) incorporated herein by reference. The fibrosarcoma B 10.2 line was induced by subcutaneous implantation of a parrafin pellet containing 5 mg of methylcholanthrene, and the B10.5 line was induced by chronic exposure to ultraviolet radiation. The tumor cell lines were maintained in vitro in α-modified MEM containing 5% FBS, 2nM L-glutamine, 50 U/ml penicillin and 50 µg/ml streptomycin. **Recombinant human flt3-L (10µg/injection) was administered on a daily basis over a 19-day period (unless otherwise noted) by subcutaneous injection in a total volume of 100 µl.** Control mice were similarly injected with a similar volume of buffer containing 100 ng MSA. Tumor growth rates were determined by plotting the tumor size versus time after tumor challenge. Tumor size was calculated as the product of two perpendicular diameters, measured by calipers, and is expressed as the mean tumor size of only those mice beating a tumor within a particular treatment group. The number of mice bearing tumors compared to the number challenged for each treatment group at the termination of an experiment are shown in the data below.

While the instant specification as filed describes "administering Flt3-ligand prior to, concurrently or with or subsequent to administration of an antigen to a patient for immunization purposes" (e.g., see page 10, paragraph 1 of the instant specification) as well as "typical dosing of Flt3-ligand in the ranges from about 10 µg per square meter to about 1000 µg per square meter" (e.g., see pages 12-13, overlapping paragraph of the instant specification)

as well as the administration of recombinant human Flt3-L on a daily basis over a 19-day period (e.g., see Example 3);

there is insufficient written support for administration of Flt3-L for "14 days or for a period of 14-19 days", as currently claimed.

The description of generating dendritic cells in vitro (versus the claimed in vivo methods) with a combination of cytokines, including Flt3-L as set forth in Example 1 does not provide sufficient written support for administering Flt3-L in vivo for either "14 days or for a period of 14-19 days", as currently claimed.

Therefore, applicant has not pointed out sufficient description in the specification as filed as to the phrase "a period of 14-19 days" in the specification as filed, as currently claimed.

Rather, it appears that applicant has relied upon the general terms and disclosure of dosing and modes of administration of Flt3-ligand, the use of an in vivo experimental model and the generation of in vitro culturing of dendritic cells to set forth a new "limitation".

The instant claims now recite limitations which were not clearly disclosed in the priority applications as well as the specification as-filed, and would have changed the scope of the priority applications and do change the scope of the instant disclosure as-filed.

It cannot be said that a subgenus is necessarily described by a genus encompassing it and a species upon which it reads. See In re Smith 173 USPQ 679, 683 (CCPA 1972) and MPEP 2163.05.

The specification as filed does not provide a sufficient written description of the newly added "for a period of 14 to 19 days". The specification does not provide sufficient blaze marks nor direction for the instant methods encompassing the above-mentioned "duration of time", as currently recited. The instant claims now recite limitations which were not clearly disclosed in the specification as-filed, and now change the scope of the instant disclosure as-filed. Such limitations recited in the present claims, which did not appear in the specification, as filed, introduce new concepts and violate the description requirement of the first paragraph of 35 U.S.C. 112.

Applicant is required to cancel the new matter in the response to this Office Action.

Alternatively, applicant is invited to provide sufficient written support for the "limitation" indicated above.

See MPEP 714.02 and 2163.06

5. Claims 6, 7, 20, 22-24, 28, 30-35 and 40-53 rejected under 35 U.S.C. § 103(a) as being unpatentable over Lyman et al. (WO /94/28391; 1449) in view of Elliott et al. (U.S. Patent No. 5,478,556), Srivastava et al. (U.S. Patent No. 6,017,544) and Brem et al. (U.S. Patent No. 5,626,862) essentially for the reasons set forth in the previous Office Actions and in further view of newly added Gillis (U.S. Patent No. 5,199,942) and Kaushansky (U.S. Patent No. 6,316,254).

Applicant's arguments in conjunction with certain legal citations, filed 11/19/2007, have been fully considered but are not found convincing essentially for the reasons of record.

Applicant argues that the hemopoietic stem and/or progenitor cells must be exposed to Flt3-ligand for an extended period in order to generate an increase in the number of dendritic cells in the patient, which is a feature not taught or suggested by the prior art.

Gillis (U.S. Patent No. 5,199,942) and Kaushansky (U.S. Patent No. 6,316,254) have been added to provide for administering cytokines of interest over an extended period of time in order to expand hemopoietic stem and/or progenitor cells in patients at the time the invention was made.

For example, Gillis teaches in vivo administration of cytokines, including GM-CSF, to stimulation and proliferation of hemopoietic stem cells, including an Example of treating patients in vivo with an engraftment growth factor for 7 to 21 days after administration of cells (e.g., see Detailed Description of the Invention, including column 6, paragraph 3 and Example 8 on column 12 as well as Claims 1, 9 and 16).

Kaushansky teach the administration of cytokines, including GM-CSF, over a period of up to 28 days following a bone marrow transplant in patients to increase the proliferation and differentiation of progenitor cells or lymphocytes of interest (e.g., see column 16, paragraph 1).

Applicant's arguments and the examiner's rebuttal are essentially the same of record.

Again, applicant asserts that the examiner fails to consider that none of the references teach or suggest alone or in combination the use of Flt3-ligand in an amount sufficient to an increase in the number of dendritic cells as claimed.

Again, applicant distinguishes the amount of time that Lyman expanded hemopoietic cells in cultures with Flt3-ligand with the amount of time relied upon in the instant Examples with respect to both in vitro culture conditions associated with generating large number of dendritic cells in vitro or in vivo.

Applicant argues that the hemopoietic stem / progenitor cells must be exposed to Flt3-ligand for an extended period of time to generate an increase in the number of dendritic cells in a patient.

In focusing on the recitation of "a sufficient amount" and "a sufficient duration of time", applicant asserts that there is no motivation in the art to achieve the claimed invention, such as augmenting the tumor-specific immune response by increasing the number of dendritic cells.

In turn, applicant submits that the lack of motivation renders the claims unobvious whether or not there are unexpected results.

Again, applicant, in combination with various legal decisions, asserts that the combination of Flt3-ligand and GM-CSF administered in combination with a particular antigen (BLP25) provided unexpectedly superior results in terms of preventing formation of tumors.

Again, as pointed out previously, applicant's basis for this assertion of unexpected results appears to be based upon one particular experimental model study.

It is noted that point #4 of the Conclusions of the Study are that the results look encouraging and it would be worthwhile to repeat and extend this experiment.

Similar statements are made at the end of the Discussion of the study.

Also, it is noted that the Discussion of the Study indicates that lipid A rapidly enhances dendritic cell maturation.

Therefore, applicant is relying upon a single experimental study as well as the contribution of lipid A in the study to assert unexpected results of the combination of FLT3-ligand and GM-CSF, as broadly claimed.

Again, while applicant relies upon an extended period of time to generate an increase in the number of dendritic cells in a patient, the specification as filed does not appear to define "the amount sufficient to generate an increase in the number of patient's dendritic cells".

Giving the claims the broadest reasonable interpretation, see In re Zletz, 893 F.2d 319, 321, 13 USPQ2d 1320, 1322 (Fed. Cir. 1989) (during ex parte prosecution, claims are to be given their broadest reasonable interpretation consistent with the description of the invention in the specification),

the claims read on methods of administering Flt3-ligand in "effective amounts" and "a period of 14-19 days" that generates an increase in the number of the patient's dendritic cells.

The newly added references of Gillis (U.S. Patent No. 5,199,942) and Kaushansky (U.S. Patent No. 6,316,254) provide for the known practice of administering cytokines of interest to increase the number and differentiation of hemopoietic stem and/or progenitor cells of interest in patients, including extended periods of three to four weeks after the administration of the hemopoietic cells of interest.

The following is reiterated for applicant's convenience.

The claims read on any measurable increase in the number of the patient's dendritic cells that augment tumor-specific immune responses in a patient.

Thus, all that is required is that the prior art methods elicit any measurable level of augmenting tumor-specific immune response by increasing the number of dendritic cells.

Any increase or mobilization of a patient's dendritic cells via the administration of Flt3-ligand would meet the sufficient or effective amounts of Flt3-ligand to meet the claim (e.g. see page 10, paragraph 1 of the instant specification).

The typical dosages of Flt3-ligand ranging from about 10 – about 1000 μg per square meter indicated on pages 12-13, overlapping paragraph of the instant specification are the same exact dosages described by page 26, paragraph 1 of Lyman et al. (WO 94/28391).

Both disclosures provide for the same determination and scaling of dosing to provide for effective amounts of Flt3-ligand alone or in combination with other active materials.

Lyman et al. also provides for the administration of Flt3-ligand alone, sequentially or in concurrent combination with other cytokines listed therein, including GM-CSF as well as simultaneously or subsequent to the infusion of cells in patients (see Example 13, particularly page 43, paragraph 1).

It is noted that Lyman et al. teach that such procedures are useful for the expansion of hemopoietic cells as well as the ability to elevate a patient's immune response (see Background of the Invention and the Summary of the Invention on pages 1-6 of the Lyman et al.).

Although applicant focuses on "the amount sufficient for a sufficient duration to generate an increase in the number of patient's dendritic cells",
applicant has not sufficiently distinguished the dosing and modes of administration that appear to be the same or nearly the same as encompassed by the instant claims and as disclosed in the specification as filed.

"Expected beneficial results are evidence of obviousness of a claimed invention, just as unexpected results are evidence of unobviousness thereof." In re Gershon, 372 F.2d 535, 538, 152 USPQ 602, 604 (CCPA 1967). See MPEP 716.02(c).

Also, see KSR International v. Teleflex Inc., U.S. Supreme Court No. 04-1350 (April 30, 2007) for guidance as to the determination of obviousness.

Here, the prior art clearly provides for providing GM-CSF can lead to the elimination of tumor cells in a patient in a potent and specific manner and this is done in combination with other chemotherapeutic agents such as cytokines, which can have broad immunoregulatory properties (e.g. see Brem et al., Combinations with other biologically active compounds on columns 8-9).

In addition, the prior art recognized the advantages of providing stimulation to various compartments of the recipient to maximize the physiological and therapeutic response (e.g. see Background of the Invention of Elliott et al. and Formulation and Administration of the Complexes on columns 11-12 of Srivastava as well as the citation of Brem et al. herein).

The prior art as indicated previously and herein provide for combining various bioactive agents, including cytokines, including GM-CSF in combination with other cytokines, including multiple or subsequent administration of said bioactive substances / cytokines to maximize physiological and therapeutic responses (e.g., see columns 11-12 of Elliott et al.; columns 8-9 of Brem et al.; and columns 1-12 of Srivastava et al.).

In addition, all of the references are consistent with the instant specification that dosages and modes of administration depend on variables known and practiced in the art at the time the invention was made.

Also, as indicated previously and provide herein, the prior art clearly provides for the use of cytokines such as GM-CSF to expand the numbers and augment the activity of dendritic cells in generating tumor-specific immune responses.

For example, the prior art clearly provides for providing GM-CSF can lead to the elimination of tumor cells in a patient in a potent and specific manner and this is done in combination with other chemotherapeutic agents such as cytokines which can have broad immunoregulatory properties (e.g. see Brem et al., Combinations with other biologically active compounds on columns 8-9).

Therefore, the prior art recognized the advantages of providing stimulation to various compartments of the recipient to maximize the physiological and therapeutic responses and that such advantages could be accomplished with cytokines, such as Flt3-ligand and GM-CSF and combinations with cytokines thereof, that enhance the growth and /or elaboration of hemopoietic or immune-type cells in cancer patients.

The effective amounts provide by the prior art either with respect to Flt3-ligand, GM-CSF or combinations of cytokines are consistent with that encompassed by the broadest reasonable interpretation of the claimed methods. Similarly to applicant's assertions, the prior art provides for multiple administration of effective amounts of cytokines as well as known practices by the ordinary artisan to achieve the therapeutic effects of stimulating hemopoietic cells, including dendritic cells, in achieving anti-tumor immune responses in cancer patients at the time the invention was made and that combinations of such cytokines were expected to maximize such desired endpoints.

Applicant's reliance upon combining cytokines to increase responses is consistent with the same or similar teachings of the prior art. Hemopoietic and immune-type cells, including stem / progenitor cells, express multiple receptors for growth factors and that interactions with one or more of these receptors via the growth factors influence the growth and development of the cells. Consistent with the prior art teachings of combining cytokines to maximize response, it has been long appreciated by the ordinary artisan that combinations of growth-promoting agents or factors were necessary to elicit / maximize desired responses by hemopoieitic / immune-type cells.

Applicant's reliance upon combining cytokines such as Flt3-ligand and GM-CSF to increase responses when compared to each cytokine acting alone is consistent with the prior art teachings that maximizing physiological and therapeutic responses was expected to be achieved by combinations of cytokines.

The strongest rationale for combining references is a recognition in the art that some advantage or expected beneficial result would have been produced by their combination. This recognition may be an expressed statement in a reference, an implication that can be drawn from one or more references or a convincing line or reasoning based upon established principles or legal precedent.

One of ordinary skill in the art at the time the invention was made would have been motivated to select a combination of cytokines, including Flt3-L and GM-CSF in combination with tumor antigens to treat human cancer; given the properties of said cytokines to augment immune responses including augmenting immune responses to cancer antigens and to stimulate hemopoietic cells to alleviate the effects of chemotherapy and radiation therapy in cancer patients.

While Lyman et al. may differ from the claimed methods by not disclosing the known administration of a tumor antigen to a cancer patient to induce an immune response to the desired tumor antigen and that the administration of Flt3-L and/or GM-CSF would lead to an increase in the number of dendritic cells per se.

Lyman et al. teach the administration of sufficient / effective amounts of Flt3-L to cancer patients that are consistent with instant disclosure and broadest reasonable interpretation of the claims.

In contrast to applicant's assertions, the prior art clearly provides for generating tumor-specific immune responses that include, in part, the increase in the number of the patient's dendritic cells as well as the increase of anti-tumor responses in said patients.

Again, applicant is reminded that the reason or motivation to modify the reference may often suggest what the inventor has done, but for a different purpose or to solve a different problem. It is not necessary that the prior art suggest the combination to achieve the same advantage or result discovered by applicant. In re Linter, 173 USPQ 560 (CCPA 1972) (discussed below); In re Dillon , 16 USPQ2d 1897 (Fed. Cir. 1990), cert. denied , 500 U.S. 904 (1991) (discussed below).

Although Ex parte Levengood, 28 USPQ2d 1300, 1302 (Bd. Pat. App. & Inter. 1993) states that obviousness cannot be established by combining references "without also providing evidence of the motivating force which would impel one skilled in the art to do what the patent applicant has done " (emphasis added), reading the quotation in context it is clear that while there must be motivation to make the claimed invention, there is no requirement that the prior art provide the same reason as the applicant to make the claimed invention.

Therefore, the reason or motivation to combine may often suggest doing what the inventor has done, but for a different purpose or to solve a different problem than that asserted by the inventor. See MPEP 2144.

Therefore the rejection of record is maintained for the reasons of record and addressed above and reiterated for applicant's convenience.

The instant claims are drawn to methods of augmenting immune responses in cancer patients with FLT3-ligand and GM-CSF.

Lyman et al. teach methods of treating cancer patients by administering FLT3-L in combination with other cytokines, including GM-CSF including treating intestinal damage resulting from irradiation and chemotherapy and stimulating immune responses as well as hemopoietic cells to improve the quality of life of a patient (see entire document; Background of the Invention; Summary of the Invention, including Claims). Lyman et al. teach the FLT3-L and its recombinant forms and sequences encompassed by the claimed invention (See Detailed Description of the Invention and Examples).

Lyman et al. differs from the claimed methods by not disclosing the known administration of a tumor antigen to a cancer patient to induce an immune response to the desired tumor antigen and that the administration of FLT3-L and/or GM-CSF would lead to an increase in the number of dendritic cells per se.

Both Elliott et al. and Srivastava teach that GM-CSF teach the known administration of GM-CSF with tumor antigens to simulate the immune system.

Elliott et al. teach the vaccination of cancer patients with tumor associated antigens mixed with cytokines, including GM-CSF, including the stimulation of antigen-processing (see entire document, Background of the Invention, Summary of the Invention, Detailed Description of the Invention). Both the tumor associated antigens and the GM-CSF can be administered at various times (see Summary of the Invention).

Srivastava teach methods of augmenting cancer vaccines with cytokines including GM-CSF (see entire document; including Summary of the Invention, including column 4, paragraph 6; Detailed Description, including column 12, paragraph 3; Claims.). Srivastava teach compositions comprising cancer cells as well as cancer antigens serve as sources for immunization against tumor antigens of interest (See entire document, including Background of the Invention, Summary of the Invention and Detailed Description of the Invention). In addition to combining cancer therapies, including surgery, radiation therapy and chemotherapy (columns 5-6, overlapping paragraph), dosages and modes of administration depend on variables known and practiced in the art at the time the invention was made (e.g. see columns 11-12, Formulation and Administration of the Complexes). Srivastava teach that a number of tumor types, including fibrosarcoma, can be treated (see column 6, paragraphs 4-5).

Brem et al. teach the GM-CSF is a cytokine that systematically activate cytotoxic T lymphocytes which have shown to lead to the elimination of tumor cells in a potent and specific manner, by stimulating the growth and activity of several myeloid cells and playing a critical role in the migration and development of professional antigen presenting cells such as dendritic cells (see column 8, paragraph 2).

Given the teachings of combining FLT3-L and GM-CSF to treat cancer by Lyman et al. in combination with the teachings of Elliott et al. and Srivastava et al. that GM-CSF was potent in cancer vaccination, one of ordinary skill in the art would have combined FLT3-L, GM-CSF and tumor antigens to stimulate the hemopoietic and immune system of cancer patients, including the vaccination to tumor associated antigens. Given the teachings of stimulating the hemopoietic and immune systems with FLT3-L and GM-CSF with the teachings of administering tumor antigens to activate immune responses and antigen presentation, one of ordinary skill in the art would have had an expectation of success that the administration of FLT3-L and GM-CSF would increase the number

of dendritic, as evidenced by the teachings of Brem et al. that GM-CSF activates immune responses via dendritic cells.

Given the teachings of the prior art to treat and augment immune responses in cancer patients and that the administration of cytokines and tumor antigens were based on variables and procedures known and practiced by the ordinary artisan, it would have been obvious to one of ordinary skill in the art at the time the invention was made to administer tumor antigen at various times with respect to cytokine administration, including the administration of tumor antigen prior, concurrently and after cytokine administration.

One of ordinary skill in the art at the time the invention was made would have been motivated to select a combination of cytokines, including FLT3-L and GM-CSF in combination with tumor antigens to treat human cancer; given the properties of said cytokines to augment immune responses including augmenting immune responses to cancer antigens and to stimulate hemopoietic cells to alleviate the effects of chemotherapy and radiation therapy in cancer patients.

From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicant's arguments have not been found persuasive.

Here, the prior art provides sufficient motivation and expectation of success in arriving at the same manipulative steps as the claimed invention in treating patients having cancerous or neoplastic disease.

6. No claim is allowed.

7. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a).

Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (571) 272-0844. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Eileen O'Hara can be reached on (571) 272-0878.

The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Phillip Gambel, Ph.D., J.D.
Primary Examiner
Technology Center 1600
February 4, 2008